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Michael O. Leavitt, Administrator  
U.S. Environmental Protection Agency  
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**PETA**

PEOPLE FOR THE ETHICAL  
TREATMENT OF ANIMALS

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Re: Comments on the HPV test plan for hydroxybenzenesulfonic acid

Dear Administrator Leavitt:

The following comments are on the test plan for hydroxybenzenesulfonic acid (CAS no. 1333-39-7), submitted on behalf of the Aromatic Sulfonic Acids Association (ASAA). These comments are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

The ASAA states that no mammalian toxicity data other than for acute toxicity are available and that a combined repeated-dose, developmental and reproductive study (OECD no. 422) must therefore be carried out. We note that this is yet another essentially non-toxic compound in the HPV program for which another 675 animals are to be condemned to death.

In addition to our objection to the check-the-box mentality inherent in further testing of this chemical, we have the following concerns regarding the ASAA's planned mammalian study:

- (i) The ASAA has made no attempt to estimate the toxicity of hydroxybenzene- sulfonic acid on the basis of the known toxicities of related compounds. The two components of the hydroxybenzenesulfonic acid molecule are a phenol and a sulfonate group, the toxicity of both of which has been thoroughly established. In addition, HPV test plans have been submitted for numerous sulfonates and substituted phenols. The ASAA itself submitted a test plan for benzenesulfonic acid (with a hydrogen atom where hydroxybenzenesulfonic acid has a hydroxyl group), and uses p-toluenesulfonic acid (with a methyl group at that locus) as a surrogate for that compound. Yet the ASAA provides no rationale as to why these compounds, which are also of low toxicity, cannot be used to calculate the toxicity of hydroxybenzenesulfonic acid. We appreciate the difference between phenolic and benzene-based compounds, but the ASAA should demonstrate why a similar approach could not be used in the current situation.
- (ii) Hydroxybenzenesulfonic acid contains up to 2% phenol (test plan, p. 4). Phenol is a much more toxic compound than hydroxybenzenesulfonic acid. In addition, phenol is highly caustic, and is also severely toxic or lethal at low doses in certain hypersensitive human individuals; for example, ingestion of 4.8 g killed one person in less than 10 minutes (HSDB). Therefore, as exposure to hydroxy-benzenesulfonic acid almost invariably involves exposure to phenol, the toxicity of the former compound is largely academic.

- (iii) The ASAA provides very little information about the use of hydroxybenzene-sulfonic acid, stating only that it is “a chemical intermediate and a resin binding catalyst” (test plan, p. 3). Given the fact that this compound is of low toxicity (the LD<sub>50</sub> values are greater than 1.5 g/kg), the relevance of additional detailed toxicity data depends largely on the actual or potential human exposure. For example, since hydroxybenzenesulfonic acid is often a chemical intermediate, information about whether it is a closed-system intermediate in these cases should be provided. We also note that if there are genuine concerns about the chronic or reproductive and developmental toxicity of hydroxybenzene-sulfonic acid, the first step in assessing these areas should be to consider exposure information and to carry out epidemiology studies if needed.
- (iv) We are concerned about the possibility of marked inter-individual variation in toxicity due, for example, to hypersensitivity which is frequently associated with phenolic compounds. If hypersensitivity occurs, it is likely to be the most dangerous type of toxicity due to hydroxybenzenesulfonic acid, but it will be almost impossible to detect using animal experiments. We therefore again suggest that all available data on exposure and possibly related symptoms should be reviewed in detail before deciding which types of toxicity have real-world importance.

If the ASAA insists on conducting the OECD 422 as planned, we request that it also conduct the rodent embryonic stem cell test (EST) in parallel with the OECD 422. This *in vitro* embryotoxicity test method has been validated by the European Centre for the Validation of Alternative Methods, and the Centre’s Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). We have repeatedly provided validation and SOP references and suggested that, in this *screening level* program, a positive result found in the EST should warrant the substance's treatment as a developmental toxicant/teratogen and that no further testing should then be carried out for the HPV program.

We have also urged individual companies to consider the use of this test in parallel, and several have agreed to do so in order to help build the database for industrial chemicals for eventual validation of the EST in the U.S. (Please note that the cost of the EST is a fraction of the cost of the OECD 421/422.) We hope to receive a positive response that the ASAA will also run the EST for this substance if it goes ahead with reproductive/developmental toxicity testing on animals. We would be happy to provide further information on a local laboratory that conducts this test commercially.

With regard to the cell type to be used in the proposed *in vitro* chromosomal aberration test (OECD Test Guideline 473), the ASAA does not specify the cells it intends to use. We urge the ASAA to use human lymphocytes. However, should it choose to use Chinese hamster ovary (CHO) cells, it should ensure that any cells used are from an established cell line rather than from primary tissue.

With respect to aquatic toxicity, the ASAA is to be commended for having used ECOSAR to predict the toxicity of hydroxybenzenesulfonic acid to algae, invertebrates and fish. The result

was that hydroxybenzenesulfonic acid is not expected to be toxic to any of these organisms (Appendix, p. 10) and on this basis the ASAA has reached the following conclusion:

Two of the species should be tested. If the resulting measured data are in agreement with the calculated data no further testing is warranted; if the resulting measured data disagree with the calculated data also the third species has to be tested (test plan, p. 5).

We agree with the principle that no further testing is needed if the measured and calculated data are in agreement. However, there are several points we must add:

- (i) We hope that the two species that the ASAA intends to test first are an alga and an invertebrate. The ASAA should clarify this point.
- (ii) The ASAA's plan to carry out the test in only two species at first is not clearly stated in the summary table (test plan, p. 8). The ASAA should therefore revise this table.
- (iii) The ASAA should post the results of its two first ecotoxicity studies on the EPA's website. Then, if it intends to carry out the third study, the animal protection community should have the opportunity to comment upon this plan.

Thank you for the opportunity to comment on this test plan. I can be reached at 757-622-7382, ext. 8001 or via e-mail at [JessicaS@PETA.org](mailto:JessicaS@PETA.org).

Sincerely,

Jessica Sandler  
Federal Agency Liaison

## References□

Genschow, E., *et al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models", *Alternatives to Laboratory Animals* 30: 151-76, 2002.

HSDB (Hazardous Substances Data Bank), "Phenol", <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~NGqDJJ:1>